REMARKS

Applicant requests reconsideration of the present application in view of these comments.

I. Status of Claims

From the language cited in the Action, it seems the examiner may have examined a prior version of the claims and not the current form, which was entered during the international phase of PCT/IB 2004/04406. In any event, the current form of the claims is presented above.

Claims 1-10 and 12-18 have been amended. Meanwhile, claims 11 and 19-35 have been cancelled. Upon entry of the proposed amendments, therefore, claims 1-10 and 12-18 will be pending.

II. Claim Objections

The examiner objects to claim 18 for lacking a period. Applicant believes the entered amendments obviate the objection.

The examiner also objects to claims 2-18 for reciting the article "A" instead of "the". Applicant has amended the claims and believes the amendments obviate the objection.

The examiner also objects to claim 35 for reciting a "use". Applicant has cancelled the claim, thus the objection is now moot.

III. Rejections Under 35 U.S.C. § 112 ¶1

The examiner rejects claims 1-18 and 35 for an alleged failure by the specification to enable a person skilled in the relevant art to practice the claimed invention. Applicant respectfully traverses the rejection.

While acknowledging that the specification enables targeted gene delivery methods comprising bispecific ligands and bacterially derived minicells containing a nucleic acid operably linked to a promoter, which yield an expression product of the nucleic acid in a targeted mammalian cell (Office action, pages 3 and 4), the examiner asserts that specification does not enable (1) methods for delivering "naked" nucleic acids or (2) methods of treating disease via gene therapy. Office Action, pages 4-9. Regarding the first ground, applicant has amended the

claims to recite that the minicells contain a therapeutic nucleic acid sequence "operably linked to a promoter" and believe the amendment obviates this aspect of the rejection.

With respect to the second ground, applicant notes that the claimed invention is not directed to methods of treating disease or gene therapy. Instead, the claims are simply directed to targeted gene delivery methodology. Accordingly, whether that methodology can be employed in a particular gene therapy protocol to ameliorate a disease state has no bearing on the enabled status of the claims.

As the examiner observed correctly, the specification does provide a detailed description of how to make and use bispecific ligands and intact, bacterially derived minicells to deliver a therapeutic nucleic acid to and achieve expression in targeted non-phagocytic mammalian cells. See application at pages 9-25, *inter alia*. To these ends, moreover, both *in vitro* and *in vivo* data from the specification, *e.g.*, in applicant's Examples 1 – 7, show that the claimed methodology is effective for a variety of non-phagocytic mammalian cells, using different types of bispecific ligands and targeting a number of different cell surface receptors.

Thus, the specification provides more than enough information on implementing the claimed methodology to satisfy the enablement requirements of §112. The rejection should be withdrawn, therefore.

IV. Rejections Under 35 U.S.C. § 102(e)

The examiner rejects claims 1-4, 7-18 and 35 for alleged anticipation by Sabbadini *et al.*, U.S. patent No. 7,183,105 ("Sabbadini"). Applicant respectfully traverses the rejection.

A. Sabbadini Fails to Teach a Method Comprising Each of the Presently Recited Elements

As an initial matter, applicant notes that nowhere does Sabbadini teach a targeted gene delivery method as presently claimed. To characterize Sabbadini as anticipatory, the examiner endeavors to recreate a method as presently claimed by cherry-picking elements from several "laundry list" disclosures in the Sabbadini text and then combining those elements, an approach that Section 102 does not countenance. In other words, the examiner errs factually in contending that Sabbadini makes accessible to the interested public a method that includes each of the presently recited elements, as Section 102 requires of an anticipatory reference. *See, e.g.*, *In re*

Hall, 781 F.2d 897, 899, 228 USPQ 453, 455 (Fed.Cir. 1986); *In re Wyer*, 655 F.2d 221, 226-27, 210 USPQ 790, 794-95 (CCPA 1981).

Under the "minicell" rubric, for instance, the Sabbadini text presents a broad genus of cell types, including eubacterial minicells, eukaryotic minicells, and archeabacterial minicells. *See* column 38, line 30 to column 41, line 15. Additionally, Sabbadini's "eubacterial minicell" category subsumes a variety of cell types, such as poroplasts, spheroplasts and protoplasts. Column 111, lines 54-62.

Another laundry list is evident in Sabbadini's characterization of the minicell as useful for delivering "therapeutic agents", which Sabbadini defines as "any type of compound or moiety". Column 7, lines 7-18. In "non-limiting" fashion, the text lists "small molecules, polypeptides, antibodies, antibody derivatives, nucleic acids, drugs, prodrugs and immunogens" in this context. *Id.* As for the "nucleic acids" subcategory, Sabbadini also states that "minicells" can comprise "antisense oliognucleotides, aptamers, antisense transcripts, ribosomal RNA, transfer RNA, molecular decoys, ribozymes or expression constructs for gene therapy," *inter alia*. Column 7, lines 45-51, and column 167, lines 31-44.

As for targeting, Sabbadini notes that a minicell may display a "binding moiety". Column 7, lines 9-12. Sabbadini broadly defines such moieties as "any chemical composition, i.e., a small molecule, a nucleic acid, a radioisotope, a lipid or a polypeptide." Column 136, lines 56-63. While Sabbadini identifies an antibody and polyethylene glycol as "non-limiting examples" of binding moieties that can be covalently attached to minicells (Column 136, lines 56-67), nothing in the cited material suggests bringing bispecific ligands into contact with any of Sabbadini's "minicells." For this reason alone, the anticipation rejection must fail.

To create some semblance of the claimed methodology, in any event, the knowledgeable reader would be obliged to pick and choose from among Sabbadini's broad genera, discussed above, even to attempt a permutation that corresponded to the combination of elements recited in applicant's claims, *e.g.*, "targeted gene delivery method," "bispecific ligands having specificity for a mammalian cell surface receptor capable of activating receptor-mediated endocytosis," "intact, bacterially derived minicell," and "containing a therapeutic nucleic acid sequence." Where, as here, "it is necessary to select portions of teachings within a reference and [to] combine them, ... anticipation can only be found if the [prior disclosed] classes of [items] are

sufficiently limited or well delineated." MPEP § 2131.02, *citing Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990).

The teachings of Sabbadini are anything but limited or well-delineated, as applicant has demonstrated. One of ordinary skill certainly could not "at once envisage" in Sabbadini's text the prescribed combination of applicant's invention. Yet this is what the PTO's own rules require for anticipation in this context. *Id.*, *citing In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

Moreover, an artisan picking and choosing from among Sabbadini's broad genera would have been dissuaded from even pursuing a method involving the recited combination of elements. As applicant's disclosure underscores, *e.g.,* at page 3, lines, 8-16, certain events must occur before a bacterially-derived recombinant minicell can deliver, to a targeted non-phagocytic mammalian cell, a therapeutic nucleic acid and achieve the production of the desired expression product, in accordance with the claimed invention. As an initial matter, (1) the recombinant minicell must recognize the target non-phagocytic mammalian cell specifically and (2) the recombinant minicell must be internalized into the target non-phagocytic mammalian cell. Conventional wisdom held, however, that large particles like intact bacterially derived minicells could not passively enter non-phagocytic mammalian cells via receptor-mediated endocytosis. (In further discussion of these themes below, applicant refers to literature detailed in the "List of Cited Publications," beginning at page 17. Copies of cited publications will be supplied shortly.)

In view of the lack of direction provided by Sabbadini and the absence of any working example, a practitioner would have been dissuaded from even attempting to deliver a therapeutic nucleic acid to non-phagocytic mammalian cells via bispecific ligands having specificity for a mammalian cell surface receptor capable of activating receptor-mediated endocytosis. Any attempt to depart from conventional wisdom and employ such a method, moreover, would have required extensive research.

B. Conventional wisdom held that large particles like intact bacterially derived minicells could not passively enter non-phagocytic mammalian cells via receptor-mediated endocytosis

The skilled artisan had no reason to have expected success in achieving events (1)-(2), *supra*, with minicell vectors. Although ligands had reportedly been used to bring a gene delivery vector into contact with a desired non-phagocytic mammalian cell, that concept cannot be generalized to all types of gene delivery vectors, particularly to minicell vectors.

For example, adenoviral vectors have been redirected to target mammalian cell-surface receptors, such as endoglin on endothelial cells, and internalized via clathrin-coated pits in the mammalian cell plasma membrane. Wickham *et al.*, 1996; Nettelbeck *et al.*, 2001; Boucher *et al.*, 2003. The clathrin-coated pits resemble a cup that envelopes the vector, but the size of the cup is understood to be a limiting factor. Clathrin-coated pits have a limited size of 85-110 nm, due to the size of the clathrin coat. Swanson & Watts, 1995. Minicells are at least 400 nm in diameter, by contrast; hence, the skilled artisan would not have expected this targeting approach to work for minicells.

Knowledge concerning other large vectors further supported the expectation that minicells would not be internalized through clathrin-coated pits. For instance, large lipoplexes (non-viral vectors up to 500 nm) preferentially enter cells by receptor- and clathrin-independent endocytosis, while smaller lipoplexes (less than 200 nm) can be internalized via a non-specific, clathrin-dependent process. Simoes *et al.*, 1999. Likewise, large viruses, such as vaccinia virus, on the order of 350 nm x 250 nm in size do not infect mammalian cells via a clathrin-coated pathway. Essani and Dales, 1979.

In a similar vein, it was known that non-phagocytic mammalian cells cannot engulf large pathogens, like bacterial cells. Only professional phagocytes like macrophages engulf such pathogens, and the engulfment process is clathrin- and receptor-independent, being accomplished by phagocytosis. The interaction of large pathogens with the cell surface induces a complex signaling cascade, leading to actin rearrangements at the plasma membrane to form a large phagocytic cup, which engulfs the bacterium. Dramsi and Cossart, 1998. Furthermore, artisans at the time had only a rudimentary understanding of the signaling cascades responsible, on

bacterial entry, for actin rearrangements at the plasma membrane. Galan, 1996; Menard *et al.*, 1996; Finlay and Cossart, 1997; Dramsi and Cossart, 1998.

Specific investigations into the effect of particle size on receptor-mediated endocytosis showed the process to be strongly size-dependent. For example, Aoyama *et al.*, 2003, studied the effect of particle size on glycoviral gene delivery and concluded that the optimal particle size for receptor-mediated endocytosis is ~25 nm. *See also* Nakai *et al.*, 2003; Osaki *et al.*, 2004. Gao *et al.*, 2005, confirmed that conclusion.

Moreover, even though bispecific ligands reportedly have been used to re-direct viral vectors, the method was not always successful in the context of gene delivery. In attempted retargeting of viruses from their native receptors to alternative receptors, many experiments have shown that cell surface attachment is insufficient for sustained viral entry and gene expression. Also, when virus envelope proteins have been modified for re-targeting, they exhibited low fusion activity, resulting in inefficient viral entry into cells. Zhao *et al.*, 1999.

Accordingly, conventional wisdom held that large particles like intact bacterially derived minicells (i.e., approximately 400 nm) could not passively enter non-phagocytic mammalian cells via receptor-mediated endocytosis.

C. Sabbadini Provides Insufficient Guidance for the Skilled Person to Effect Targeted Gene Delivery, as Claimed

In line with conventional thinking, Sabbadini, in cited example 19, advocates for i) using protoplasts, (ii) targeting via expression of antibody fusion constructs and (iii) effecting uptake via forced entry using an active invasive process. *See* U.S. Pat. No. 7,183,105, Example 19. From this perspective, it is not surprising that nothing in the cited material propounds a rationale for combining the claimed elements in the recited fashion. Moreover, it must be emphasized that Sabbadini lacks any supporting data or working examples of targeted gene delivery of any kind. In view of such a hollow disclosure and the conventional wisdom at the time of the invention, the skilled person would have been unable to effect targeted gene delivery as presently claimed.

For these reasons, at least, the rejection under Section 102(e) should be withdrawn.

V. Rejections Under 35 U.S.C. § 103

The examiner rejects claims 1, 3 and 5-6 for allegedly being unpatentable over Sabbadini in view of Nettelbeck and Coldwell. Applicant respectfully traverses the rejection.

Sabbadini's musings are discussed above. Nettelbeck, cited for allegedly teaching a recombinant antibody as a molecular bridge and the construction and use of a bispecific single chain diabody, and Coldwell, cited for allegedly teaching production of monoclonal antibodies to antigenic determinants of the O-polysaccharide of *Salmonella typhimurium* lipopolysaccharide, do not cure Sabbadini's deficiencies. For the reasons expressed above, therefore, a practitioner would have been dissuaded from even attempting to deliver a therapeutic nucleic acid to non-phagocytic mammalian cells via bispecific ligands having specificity for a mammalian cell surface receptor capable of activating receptor-mediated endocytosis. Thus, nothing in the record provides the requisite motivation for combining the recited elements in the posited fashion.

Similarly, for the reasons noted above, the skilled person would not have reasonably expected that intact bacterially derived minicells could passively enter non-phagocytic mammalian cells via receptor-mediated endocytosis. Nor would the skilled person have expected any of several other critical events to occur. In particular, beyond the successful targeting (1) and internalization (2) discussed above, additional events must occur before a bacterially-derived recombinant minicell can deliver, to a targeted non-phagocytic mammalian cell, a therapeutic nucleic acid and achieve the production of the desired expression product, in accordance with the claimed invention. These events include:

(3) The minicell must be broken down to release the therapeutic nucleic acid.

(4) Although the minicell must be broken down, at least some of the therapeutic nucleic acid must survive.

(5) The surviving therapeutic nucleic acid must escape from an intracellular vacuole, where breakdown of the minicell occurs, and must be transported to a safe place, *i.e.*, the mammalian cell cytoplasm.

(6) The therapeutic nucleic acid released into the cytoplasm must resist nucleases and survive until making it to the nucleus.

(7) The therapeutic nucleic acid must be transported to the mammalian cell nucleus, where expression of the encoded product occurs.

Additionally, all of these events must occur at a efficiency sufficient to achieve the desired effect.

A. The Skilled Artisan Could Not Reasonably Have Expected Nucleic Acids Contained Within Minicells to Escape Degradation in Vacuoles

Based on Sabbadini and the state of the prior art, the skilled artisan reasonably could not have expected to achieve events 3-5, *supra*, with minicell vectors. After being internalized by receptor-mediated endocytosis, gene delivery vectors are enclosed within endosomal or lysosomal membranes, and are therefore separated from the cytoplasm. This constitutes a significant impediment to gene delivery, especially because endosomal and lysosomal compartments can become highly caustic and degrade more than 99% of nucleic acids in a vector. Successful gene delivery vectors have mechanisms that allow nucleic acids to enter the cytoplasm, but skilled artisans would not expect minicells to have such mechanisms.

Thus, viruses have evolved sophisticated processes to enter the mammalian cell cytoplasm. Enveloped retro-viruses, such as HIV-1, gain access to the cytoplasm by direct fusion with the plasma membrane. Stein *et al.*, 1987. Non-enveloped viruses use various strategies to penetrate the endosomal membrane after endocytosis. For example, influenza viruses induce fusion of the viral and endosomal membranes, which is triggered by the acidic environment of the endosome. Marsh & Helenius, 1989. At low pH, the predominant influenza viral envelope glycoprotein hemagglutinin (HA) undergoes conformational changes, leading to the protrusion of a hydrophobic spike into the endosomal membrane that initiates membrane fusion. Bullough *et al.*, 1994. Adenoviruses also are believed to escape into the cytosol by a mechanism tied to acidification of the endosome. Low pH has several effects on the adenoviral capsid. For example, the capsid's penton protein undergoes conformational changes that expose hydrophobic regions for endosomal membrane interaction. Seth *et al.*, 1985. Additionally, intrinsic protease activity of the adenoviral capsid also seems to contribute to endosomal escape. Greber *et al.*, 1996.

For liposomal vectors, the endosomal membrane barrier continues to limit the efficiency of gene delivery. Successful release of liposomal nucleic acids is understood to result from disruption of the endo-lysosome membrane. Xu & Szoka, 1996; El Ouahabi *et al.*, 1997; Zelphati & Szoka, 1996a; Wattiaux *et al.*, 2000. Disruption of the endo-lysosomal membrane is thought to occur via transbilayer flip-flop of lipids, leading to membrane destabilization and

penetration of naked DNA into the cytoplasm. Zelphati & Szoka, 1996a; 1996b; Mui *et al.*, 2000. Studies have further demonstrated that cytoplasmic release of liposomal contents involves (a) charge neutralization of a cationic complexing agent with anionic macromolecules such as anionic lipids and proteoglycans, (b) cationic lipid-mediated fusion, and (c) membrane destabilization by pH-sensitive lipids. Wrobel & Collins, 1995; Meyer *et al.*, 1997; Clark & Hersh, 1999. Additional studies have shown that a mixture of neutral lipid (DOPE) with cationic lipid facilitates membrane disruption and increases the amount of liposomal contents released into the cytoplasm, because DOPE promotes the fusion of liposome particles with endosomal membranes. Farhood *et al.*, 1995; Fasbender *et al.*, 1997; Hafez *et al.*, 2001. Also, cationic PEI and polyamine dendrimers have been used to facilitate disruption of the endolysosomal membrane, because they have an extensive buffering capacity that provokes swelling and disruption of endosomes. Klemm, 1998; Sonawane *et al.*, 2003. Additional functionality can be incorporated into liposome vectors in the form of an endosomolytic pore forming protein from *Listeria monocytogenes*, listeriolysin O (LLO). Lorenzi and Lee, 2005. LLO is capable of breaching the endosomal membrane, thereby allowing escape of endosomal contents into the cytoplasm. Lee *et al.*, 1996.

The skilled artisan had no basis to have expected the contents of minicell vectors to escape lysosomes and avoid degradation. Rather, the art suggested that highly sophisticated mechanisms are necessary to allow a vector's contents to escape the lysosomal membrane. Minicells are non-living particles and do not possess any lysosomal membrane destabilizing functions.

Yet applicant discovered that, contrary to conventional wisdom, minicells that carry sufficient copies of plasmid DNA can function effectively as gene delivery vectors, and that some of plasmid DNA in minicells also can escape lysomal degradation.

B. The Skilled Artisan Would Not Reasonably Have Expected Minicell-Delivered Nucleic Acids, Released into the Cytoplasm, to Resist Nucleases

Based on Sabbadini and the state of the prior art, the skilled artisan had no basis for expecting that event 6, *supra*, would pertain to minicell vectors. Against foreign nucleic acids mammalian cells have innate defense systems that constitute a cytosolic barrier to successful nucleic acid delivery. This is evident from studies showing that injection of DNA plasmids into

cell nuclei results in 100–1000-fold higher target gene expression, compared with injection of DNA plasmids into the cytoplasm. Capecchi, *et al.*, 1980; Brinster, *et al.*, 1985; Lechardeur, *et al.*, 1999. The cytosolic barrier accounts for a significant part of the 100-to-1000-fold difference in target gene expression. At the core of this cytosolic barrier are cytosolic nucleases. Additionally, the movement of nucleic acids in the cytosol is limited by their size and molecular crowding effects. Lukacs *et al.*, 2000; Bicknese *et al.*, 1993. In view of such barriers, the skilled artisan would have estimated that at least 10^5 plasmids per cell are required, in the extracellular compartment, to ensure that a few DNA molecules move into the nucleus of non-mitotic cells.

Viruses have several strategies to overcome nuclease activity and low movement within the cytosol. Thus, adenoviruses, adeno-associated virus, herpes virus and other viruses exploit existing cellular components, like the actin cytoskeleton and microtubule network. Sodeik *et al.*, 1997; Suomalainen *et al.*, 1999; Douar *et al.*, 2001; Bartlett *et al.*, 2000; Seisenberger *et al.*, 2001. In particular, adenoviruses first escape the endosomes and then travel, un-encapsulated, along microtubules towards the nucleus (Seisenberger *et al.*, 2001), thereby avoiding exposure of the viral DNA to cytosolic nucleases.

The skilled artisan would not have expected minicells to have strategies for protecting therapeutic nucleic acids from nuclease degradation or for moving therapeutic nucleic acids into a mammalian cell nucleus. According to conventional wisdom, nucleic acid molecules, escaping an endolysosome, should be degraded by nucleases in the cytosol. The smaller a therapeutic nucleic acid is, the greater is the likelihood of it diffusing successfully to the nucleus and escaping cytosolic nucleases.

To the contrary, applicant discovered that highly efficient and successful gene delivery occurs through the use of bispecific antibody-targeted recombinant minicells, when the size of the therapeutic nucleic acid is as high as 10 kb, or 40-fold larger than what is currently thought to be the limit (250 bp). Additionally, applicant discovered that minicells carrying only 70-100 copies of plasmid DNA can achieve highly effective gene delivery, not only *in vitro* but also *in vivo,* whereas it was previously believed that least 10^5 plasmids per cell would be required to ensure movement of a few DNA molecules into the cell nucleus.

C. The Skilled Artisan Could Not Reasonably Have Expected That Minicell-Delivered Nucleic Acids Would Be Transported to the Mammalian Cell Nucleus, Such That Expression of The Encoded Product Occurs

Based on Sabbadini and the state of the prior art, the skilled artisan could not have reasonably expected to achieve event 7, *supra*, with minicell vectors. The nuclear envelope consists of a double lipid bilayer in which the intermembrane space is continuous with the endoplasmic reticulum (ER). This constitutes a very efficient barrier to macromolecular passage that prompted the evolution of specific nuclear transport mechanisms. The central component of nuclear transport is the nuclear pore complex (NPC), a 125-MDa complex containing as many as 50 nuclear pore proteins that are collectively referred to as nucleoporins. Wente, 2000. The function of the NPC is to allow bidirectional and specific transport of RNAs, proteins and ribonucleoprotein particles across the nuclear membrane. The NPC has a central pore about 90 nm long and 45–50 nm at the narrowest point. Stoffler *et al.*, 2003. The functional diameter of the central pore, or the maximal diameter of an object passing through the pore, however, is only about 30–40 nm. Pante & Kann, 2002.

To overcome the natural barriers to macromolecules entering the cell nucleus, viruses have developed several strategies for delivering their genetic material. Greber & Fassati, 2003. Retroviruses that are unable to infect non-dividing cells enter the nucleus upon disintegration of the nuclear envelope during mitosis. Roe *et al.*, 1993. Lentiviruses, including HIV-1, invade the nuclei of postmitotic cells. Lewis *et al.*, 1992. After nuclear entry and uncoating of the HIV-1 core, the viral RNA genome is reverse transcribed yielding the pre-integration complex (PIC) that consists of viral DNA and proteins. In contrast to HIV-1, adenovirus particles are only partially disassembled when they dock to the NPC. Adenovirus attachment to the NPC then initiates a more complete disintegration of the viral capsid, which induces nuclear import of the viral DNA genome. Trotman *et al.*, 2001. Several cellular components are necessary for adenovirus DNA import, including cytoplasmic importin h and nuclear histone H1. Whereas adenovirus particles disassemble completely during the unloading of DNA, the herpes simplex virus (HSV) genome is injected through the NPC while the virus capsid still remains intact. Tongon *et al.*, 1981. The attachment of HSV capsids to the NPC is dependent on importin h, while injection of viral DNA is mediated by other, still unidentified cytoplasmic factors.

Minicells lack such evolved strategies for transporting nucleic acids into the nucleus of mammalian cells. Skilled artisans, therefore, would not have expected minicells to be effective gene delivery vectors.

The skilled person reviewing Sabbadini's disclosure, therefore, would not have expected any of the listed events to occur, let alone all of them. The uncertainties attendant to those events equated to unsolved problems in the art, and the skilled artisan would not have accepted Sabbadini as a solution to those problems. In that regard, Sabbadini contains nothing more than unsubstantiated suggestions. It lacks any supporting data or working examples of targeted gene delivery, and therefore contains no indication that the problems had been overcome or were likely to be overcome.

For these reasons, a *prima facie* case of obviousness has not been established. On this basis alone, therefore, the rejection should be withdrawn.

Yet, applicant provides still further evidence of the unobviousness of the claimed methods. In this regard, applicant notes that even today, some six years after the priority filing, the field remains skeptical of the functionality of the claimed methods to achieve targeted gene delivery. The prevailing view today is that large particles, like intact bacterially derived minicells, are too big to utilize receptor-mediated endocytosis and must use an active invasive process to induce entry in cells. *See, e.g.* Cossart and Velga (2008); Doherty and McMahon (2009). From this perspective, it is not surprising that applicant's work recently captured the cover of the prestigious journal *Nature Biotech* and also was highlighted in *Nature Reviews Cancer*. See MacDiarmid *et al.* (2009); McCarthy (2009).

It is clear, therefore, that the cited combination fails to render the claimed invention obvious. Accordingly, the rejection should be withdrawn.

VI. Rejections Under Double Patenting

The examiner provisionally rejects the pending claims under obviousness-type double patenting over U.S. applications No. 12/053,197, No. 10/492,301, No. 12/019,090 and No. 11/765,635. While acknowledging these grounds of rejection, applicant requests that the examiner hold them in abeyance until such time as he indicates allowable subject matter. Should a concern remain in this regard, then applicant will address the merits of the rejection.

Applicant requests an early indication that this application is in allowable condition. Examiner Singh is invited to contact the undersigned directly should he feel that any issue requires further consideration.

The Commissioner is hereby authorized to charge any additional fee, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicant petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of the relevant fee from the deposit account.

Respectfully submitted,

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